REMARKS

In the Office Action dated June 1, 2007, claims 1-19, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 1-19 remain in this application.

The specification was objected to by the Examiner on two grounds:

(i) Page 1 was not numbered. In this amendment, page 1 has been deleted and a substitute first page including a page number is enclosed.

(ii) The disclosure contains a trademark. The terms "Taxol" and "Taxotere" are acknowledged as trademarks on page 5. The symbol ® has been added to each subsequent use of the trademarks on page 6 and 7.

In view of the above amendments, applicants request that these objections be withdrawn.

Claims 1-19 were objected to due to a gap in formula 1. Claim 1 has been amended to replace the structure shown for formula 1 with a structure which does not include a gap between the right-hand phenyl group and the methylene group. In view of this amendment, applicants request that this rejection be withdrawn.

Claims 1-7 and 19 were rejected under 35 USC §112, second paragraph as indefinite due to the language "sufficient time to permit". Step (b) of claim 1 indicates that the time is sufficient to permit binding of intracellular histamine. As indicated in the present disclosure (paragraphs [0015] and [0016]), the administration of the diphenyl compound to the patient prior to administration of the chemotherapeutic agents is necessary in order to permit the diphenyl compound to inhibit binding of intracellular histamine in normal and malignant cells and thereby, in effect, shut down the proliferation of the normal cells, but increase proliferation of malignant cells. One skilled in the art could determine the length of time required to inhibit binding of intracellular histamine (i.e. prior to administration of the chemotherapeutic agents) depending on the diphenyl compound, its mode of administration and the size of the patient. As indicated in paragraph [0016] of the present application, generally, the diphenyl compound is administered to the patient about 30 to about 90 minutes, preferably about 60 minutes, prior to administration of the chemotherapeutic agents. The specification, addressed to a person skilled in the art, therefore, provides the basis for the time period and a guideline to the time period. Applicant respectfully points out that similar language has been found acceptable in other US Patents, for example, claim 1 of US Patent No. 5,859,065. In view of the above discussion, applicants request that this rejection be withdrawn.

Claims 1-19 were rejected under 35 USC 103(a) as unpatentable over Brandes US 5,618,846 taken with Vincent US 2004/0248986 and Khoo et al Journal of Clinical Oncology, Vol. 17, March 11, 1999: 3431-3457 in view of Beer et al, The Prostate 45:184-193 (2000). The present invention is concerned with a method of

neoadjuvant chemotherapy in patients with inflammatory breast cancer or T3 or T4 breast cancer. As is explained in the disclosure, in T3 or T4 breast cancer, chemotherapeutic agents are administered prior to surgical removal of the tumor in order to reduce the size of tumor. Inflammatory breast cancer infiltrates the lymphatics of the skin and is usually a diffuse tumor of high malignancy.

The present inventor has a number of patents identified in the present specification dealing with an improved method for the *in vivo* chemotherapeutic treatment of cancer in which there is first administered a compound which inhibits normal cell proliferation while promoting malignant cell proliferation, specifically a potent antagonist selective for intracellular histamine receptors, in an amount sufficient to inhibit the binding of intracellular histamine receptors in normal and malignant cells. Following sufficient time to permit the inhibition of intracellular histamine, a chemotherapeutic agent is administrated. An enhanced toxic effect of the chemotherapeutic agent is obtained while any adverse effect of the chemotherapeutic agent on normal cells, particularly bone marrow and gastro-intestinal cells, is significantly ameliorated.

The human test data provided in such patents is with respect to patients with advanced metastatic cancer, including metastatic breast cancer. What has surprisingly been found in a Phase II clinical trial outlined in this application is that the procedure described above, including in the cited Brandes US patent no. 5,618,846, when using the specific combination of an anthracycline chemotherapeutic agent and a taxane therapeutic agent is effective in the

neoadjuvant treatment of patients with inflammatory breast cancer or T3 to T4 breast cancer. In addition, the procedure provides an unexpected long term survival post surgery.

The office action indicates that "The Brandes reference teaches a chemotherapeutic treatment of cancer cells - inflammatory breast cancer (cell tumors are inflammatory (see col. 12, line 53 and col. 11, lines 60 to 61)." The applicant points out that while col. 11, lines 60 to 61, describe the treatment of breast cancer, col. 12, line 53 summarizes the results of Example X, which illustrates the tumor promoting and pro-inflammatory response effects of DPPE (a diphenyl compound falling within the scope of the formula in claim 1) alone. There is no cancer treatment in this Example. The passage to which the Examiner refers states:

> "The results of the experiments reported in this Example clearly shows that DPPE enhances the inflammatory response of the tumor promoter PMA" (emphasis added)."

The applicant respectfully contends that this passage does not stand for the proposition that Brandes contemplates neoadjuvant treatment of inflammatory breast cancer, as the term would be understood by a person skilled in the art and as explained above with respect to applicant's specification.

While the Brandes reference contemplates daunorubicin and doxorubicin (adriamycin), both anthracycline chemotherapeutic agents, as specific

chemotherapeutic agents, as pointed out in the office action, Brandes does not teach the use of a second chemotherapeutic agent.

The office action is correct in stating that col. 4, lines 25 to 27, contemplates that:

> "The invention is widely applicable to any size of known anti-cancer drug, which tend to be compounds specific for treatment of one type of cancer."

However, this reference does not contemplate the specific combination of the use of an anthracycline chemotherapeutic agent and a taxane chemotherapeutic agent in the treatment of inflammatory or T3 or T4 breast cancer, as required by the present claims. This reference is also silent as to neoadjuvant treatment. The office action states that:

> "The term neoadjuvant is meant as treatment that is given first to help the next treatment step go more smoothly, the type of therapy is used to shrink a large tumor before radiation or surgery."

The applicant has no argument with this characterization of "neoadjuvant". However, the conclusion that:

> "….as taught by the reference (see abstract) show the treatment is carried out to inhibit normal cell proliferation."

is incorrect. The abstract says nothing of neoadjuvant treatment. The abstract, to which the Examiner refers, describes the chemotherapy treatment of cancer cells, in which a compound which inhibits normal cell proliferation while promoting malignant cell proliferation, specifically a potent antagonist selective for intracellular histamine receptors, first is administered in an amount sufficient to inhibit the binding of intracellular histamine to the receptor in normal and malignant cells. The indicated inhibition of normal cell proliferation is irrelevant to neoadjuvant treatment but has everything to do with the chemotherapeutic treatment of cancer cells.

The Vincent reference contemplates the use of N,N-diethyl 2-[-4(phenylmethyl)-phenoxy]ethanamine mono-hydrochloride (DPPE) in cancer therapy. The DPPE is used in the treatment of patients having, or suspected of having, an aggressive cancer to extend the survival of the patient. The office action refers to the abstract as describing a neoadjuvant therapy. The office action states:

> "Vincent teaches the use of DPPE (see abstract) in the neoadjuvant treatment (as taught having an existing cancer wherein the use of surgery is needed) (see abstract)."

The abstract mentions surgery in line 8, stating:

> "The present invention further provides for the use of DPPE in the treatment of a patient suspected of having an existing cancer, wherein the use follows a surgery for treatment of a primary cancer that is estrogen-receptor negative." (Emphasis added)

Thus, the treatment contemplated in the abstract is post-surgical treatment and not a neoadjuvant therapy, are suggested by the office action.

While paragraph [0084] of Vincent contemplates the use of anthracycline chemotherapeutic agent and a taxane chemotherapeutic agent and the possibility of their respective use with or without other chemotherapeutics, the reference does not disclose or suggest the use of a specific combination of anthracycline chemotherapeutic agents and a taxane chemotherapeutic agent.

Khoo et al describes the treatment of forty-two women with anthracycline-naïve metastatic breast cancer. Chemotherapy was carried out in 21-day cycles for a maximum of seven cycles. The treatment involved an 80 minutes intravenous infusion of DPPE solution at a dose of 6 mg/kg with doxorubicin (60 mg/m^2) administered intravenously over the last 20 minutes of DPPE infusion. Khoo is silent as to the possibility of a combination of anthracyclines and taxanes and as to the neoadjuvant treatment of specific forms of breast cancer.

The Beer et al reference is concerned with the treatment of prostate cancer, an entirely male condition, whereas applicant's claims are directed to the treatment of specific forms of breast cancer, a female condition. It would appear that the Examiner is relying on Beer et al for a teaching of neoadjuvant therapy in patients undergoing prostatectomy. The office action contends that Beer et al also teaches neoadjuvant therapy of breast cancer, referring to the right-hand column of page 189. At best, this reference mentions the application of chemotherapy in early breast

cancer and adjuvant chemotherapy. There is no mention of readjuvant treatment of the specific forms of breast cancer referred to in claim 1.

The office action further asserts that Beer et al teaches combination chemotherapy including the use of DPPE with taxanes, but it is not seen where such a combination chemotherapy is described in Beer et al. In the paragraph bridging pages 186 and 187, there is described a combination therapy using DPPE and cyclophosphamide.

As the Examiner points out, the Beer et al reference refers to using taxanes, specifically paclitaxel (Taxol) and docetaxel (Taxotere). The Examiner mentions that both taxanes are used at a dosage of 75 mg/M^2. However, as is apparent from the last paragraph in the left-hand column of page 187, it is docetaxel which is used at a dose of 75 mg/M^2 while paclitaxel is administered at a dose of 135 to 175 mg/M^2.

It is emphasized that the essential teaching with respect to chemotherapy treatment in Beer et al is directed to the treatment of hormone-refractory prostate cancer. It is not seen that a person skilled in the art, seeking a treatment for inflammatory breast cancer or T3 or T4 breast cancer would look to a reference directed to the treatment of hormone-refractory prostate cancer.

While the Beer et al reference refers to neoadjuvant treatment of hormone-refractory prostate cancer, applicant contends that there is no suggestion to use the combination of an initial DPPE treatment of an anthracycline chemotherapeutic agents and taxane chemotherapeutic agents in the treatment of breast cancer. It is

noted that none of Brandes, Khoo et al or Beer et al refer to any treatment leading to increased survival.

It is apparent from the above discussion that the combination of cited references does not suggest or disclose the present invention. The present invention, as defined in claim 1, involves a specific treatment for a specific breast cancer condition involving the use of a specific combination of anthracycline chemotherapeutic agents and taxane chemotherapeutic agents.

In the Office Action, the Examiner states:

> "Brandes, lacks the teaching of specifically incorporating a taxane, but teach that any chemotherapeutic agent can be used, thus one of ordinary skill in the art would be motivated to combine the Beer et al dosage for a docetaxel/paclitaxel."

As already discussed, the Brandes reference is entirely silent as to neoadjuvant treatment and the use of any combination of different chemotherapy agents, let alone the specific combination of anthracyclines and taxanes. Since Beer et al is entirely concerned with the treatment of hormone-refractory prostate cancer, there is no indication that taxanes might be useful in the neoadjuvent treatment of breast cancer and certainly not in combination with anthracyclines.

The Examiner then states:

> "One of ordinary skill in the art would have been motivated to use [as] a chemotherapeutic agent and a taxols to administer the treatment dosage as taught by both references and expect a successful result because both references teach the ranges of the drug and combination is taught by Brandes."

There is no motivation provided by Beer et al to use taxanes in combination with anthracyclines in a neoadjuvant treatment of a specific breast cancer condition.

The Examiner concludes:

> "One of ordinary skill in the art would have been motivated to combine the above cited prior art and a taxol (paclitaxel) as taught by Beer because as taught by Brandes, the invention is widely applicable to any type of chemotherapeutic drug (see col. 4, lines 25 to 27) therefore nothing unobviousness is seen in the combination."

Notwithstanding the general statement in Brandes with respect to chemotherapy agents, the combination of cited prior art fails to disclose or suggest the specific use of a combination of an anthracycline chemotherapy agents and a taxane chemotherapeutic agent for the neoadjuvant chemotherapy in patients with inflammatory breast cancer or T3 or T4 breast cancer, as claimed in claim 1. Accordingly, it is submitted that claims 1 to 19 are patentable over the combination of cited prior art and the applicants requests that this rejection be withdrawn.

Claims 1 to 19 were provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1 to 17 of US Patent Application No. 10/526,563 in view of Khoo et al. US Patent Application No. 10/526,563 has been abandoned, so the provisional rejection is moot.

Claims 1 to 19 were provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1 to 21 of US Patent Application No. 10/527,682 in view of htpp://www.breastcancer.org/dia_pict_staging.html. US Patent Application No. 10/527,682 has been abandoned, so the provisional rejection is moot.

Applicants respectfully submit that all of claims 1-19 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

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TITLE OF INVENTION

NEOADJUVANT TREATMENT OF BREAST CANCER

FIELD OF THE INVENTION

[0001] The present invention relates to the treatment of breast cancer.

BACKGROUND OF THE INVENTION

[0002] One of the major chemotherapeutic treatments is that of malignant growth (cancer) in humans. The objective of chemotherapy is the total extermination of clonogenic tumor or malignant cells, with minimal damage to the patient. However, one of the major limitations of the chemotherapeutic approach for managing human cancer is the general inability of anticancer drugs to discriminate between normal and tumorous cells. Anti-neoplastic agents have the lowest therapeutic indicies of any class of drugs used in humans and hence produce significant and potentially life-threatening toxicities. Certain commonly-used anti-neoplastic agents have unique and acute toxicities for specific tissues. For example, the vinca alkaloids possess significant toxicity for nervous tissues, while adriamycin has specific toxicity for heart tissue and bleomycin has for lung tissue. In general, almost all members of the major categories of anti-neoplastic agents have considerable toxicities for normal cells of gastrointestinal, epidermal and myelopoietic tissues.

[0003] Generally, the dose-limiting consideration for chemical management of cancer in humans is the toxicity that anti-neoplastic agents have for the pluripotent stem cells of myelopoietic tissue. This toxicity arises from the fact that most anticancer drugs function preferentially against proliferating cells but with no significant capacity to discriminate between cycling normal and cycling tumor tissues.

[0004] In certain types of locally-advanced breast cancer, specifically inflammatory or T3 to T4 breast cancer, there is applied a treatment with chemotherapeutic agents prior to surgical removal of the tumor, in order to reduce the size of tumor. T3 tumors are tumors sized >3 and <4 cm. T3 tumors may be operable or inoperable depending on where in the breast they are located. For example, they are often inoperable if close to the chest wall, especially in small breasts. T4 tumors are tumors sized >4 cm and generally are inoperable. Inflammatory breast cancer infiltrates the lymphatics of the skin, is usually a diffuse tumor and very high grade in term of malignancy.